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ABSTRACT BOOK

New challenges of viral hepatitis

OC 74 DECLINE OF PREVALENCE OF RESISTANCE ASSOCIATED SUBSTITUTIONS TO NS3 AND NS5A INHIBITORS AT DAA-FAILURE IN HEPATITIS C VIRUS IN ITALY OVER THE YEARS 2015 TO 2018

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Background: A minority of patients fail to eliminate HCV and resistance-associated substitutions (RASs) are commonly detected at failure of interferon-free DAA regimens.

Material and methods: Within the Italian network VIRONET-C, the prevalence of NS3/NS5A/NS5B RASs was retrospectively evaluated in patients who failed an EASL recommended DAA-regimen in 2015-2018. NS3, NS5A and NS5B Sanger sequencing was performed using homemade protocols. The geno2pheno system was used to infer HCV-genotype/subtype and predict drug resistance. The changes in the prevalence of RASs over time were evaluated using the chi-square test for trend, predictors of RASs at failure were analysed by logistic regression.

Results: We included 386 real-life HCV pts failed to recommended DAA regimens: 92% (271/294) Italians, 75% (286/384) males, median age was 56 years (IQR 52-61); 106 (28%) were treatment-experienced: 91 (86%) with IFN-based treatments, 26 (25%) with DAA-based regimens. Metavir fibrosis stage was F4 in 76% (245/322), 65% (240/369) had clinical cirrhosis. Patients with HIV and HBV coinfection were 10% (33/317) and 8% (6/72), respectively. HCV genotype (G) was G1b in 122 pts (32%), G3a 103 (27%), G1a 97 (25%), G4d 30 (8%), G2c 19 (5%), G3h 5 (1.3%), G4a 4 (1%) and 1 (0.3%) each for G3g, G4n/o/v. DAA regimens were: LDV/SOF in 115 (30%), DCV/SOF in 103 (27%), 3D in 83 (21%), EBR/GRZ in 32 (8%), VEL/SOF in 29 (7%), GLE/PIB in 18 (5%) and 2D in 6 (2%); ribavirin was administered in 123 (32%). Antiviral treatment was completed by 352 pts (91%), while 34 (9%) discontinued prematurely. The NS5A fasta-sequence was available for all pts, NS5B for 361 (94%), NS3 for 365 (95%).

The prevalence of any RASs was 87%, namely 78/135 (58%) in NS3, 303/359 (85%) in NS5A, 114/286 (40%) in NS5B (Tab 1).

The prevalence of any RASs significantly declined from 2015 to 2018 (100%, 13/13 vs 81%, 101/125, p=0.01): NS5A RASs from 100%, 13/13 to 76%, 76/100 (p<0.001), NS3 RASs from 88%, 7/8 to 44%, 28/63 (p=0.02), while NS5B RASs remained stable.

Independent predictors of any RASs included liver cirrhosis/advanced fibrosis (AOR 3.72, CI 95% 1.51-9.17, p=0.004) and genotype (G2 vs G1a AOR 0.01, CI 95% 0.0-0.3, p<0.001; G3 vs G1a AOR 0.22, CI 95% 0.05 -0.98, p<0.047; G4 vs G1a AOR 0.13, CI 95% 0.03-0.63, p<0.011), with a modest effect scored for past treatment (AOR 3.45, CI 95% 1.00-11.92, p=0.05), after adjusting for DAA regimen and year of genotype.

Notably, full activity was predicted for GLE/PIB in 75.9% of cases and for at least two components of VEL/SOF/VOX in 59% of cases and no case with full-resistance to either regimen was found (Tab 2).

Conclusions: Despite decreasing prevalence over the years, RASs remain a common signature at virological failure of DAA treatment, particularly in patients with the highest grade of liver fibrosis. Their distribution may vary according to genotype, so the identification of RASs after failure could play a crucial role in optimizing retreatment strategies.